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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,960	12/20/2000	Andres Metspalu	18056/00301	7252

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EXAMINER

SISSON, BRADLEY L

ART UNIT PAPER NUMBER

1634

DATE MAILED: 02/10/2003

20

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/741,960

Applicant(s)

METSPALU ET AL.

Examiner

Bradley L. Sisson

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 September 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-21, 23-27, 30 and 31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-21, 23-27, 30 and 31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 December 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 17 September 2002 has been entered.

Priority

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1634

Claims 18-21, 23-27, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

5. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC) 52 USPQ2d at 1135, bridging to 1136:

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, e.g., *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

As presently worded, the device of claims 18-21, 23-27, 30 and 31 is to be used in the analysis of any property of virtually any biological molecule linked to a fluorophore. While applicant is not claiming a method of use, the specification still must enable at least one use of

Art Unit: 1634

the claimed device. Paragraph 19, pages 5-6 of the disclosure, is the only portion of the specification found to provide suggestions as to how the device could be used, and then it is directed solely to the sequencing of nucleic acids. The disclosure does not enable the practice of sequencing via primer extension reactions, much less teach how to arrange, manipulate and interpret data generated and collected by the claimed device. As suggested in the disclosure, one is to have an array of nucleic acids primers fixed to a solid support, that primers are to anneal to the nucleic acid of interest, that the primers will be elongated and that the sequence will somehow be deduced from the label incorporated into the primer extension product. The disclosure does not address how the skilled artisan is to overcome numerous art-recognized problems in the field of nucleic acid sequencing. The art to which the invention relates, i.e., nucleic acid array art and hybridization art, has advanced to the point that certain problematic areas have been identified. In support of this position as it relates to the manufacture and use of oligonucleotide arrays, US Patent 6,077,674 (Schleifer et al.) addresses certain highly problematic areas:

While in situ synthesis is a very flexible means for producing DNA arrays, the fidelity or percentage of full-length oligonucleotides synthesized within a feature on the array is less than 100 percent. An ideal array will have only full-length oligonucleotides attached to each feature. The ideal array promotes accuracy in hybridization experiments or assays or target biological materials. If the fidelity of an in situ generated array is less than 100 percent, it typically has non full-length oligonucleotides within a feature that usually consists of shorter lengths of the correct sequence, and to a lesser degree, incorrect sequences. Typical DNA coupling efficiencies are around 97 to 99 percent for the standard phosphoramidite chemistry. For oligonucleotides that are 25 nucleotides in length, these efficiencies result in only 46 to 77 percent full-length oligonucleotides contained within a feature (0.97^{25} to 0.99^{25}). This loss of fidelity can cause chemical noise in hybridization conditions. The loss of fidelity can also lead to difficulty in interpreting the data.

Photolithography is a method used by Affymetrix in California to produce in situ arrays using procedures that are similar to those used in the semi-conductor industry. In procedure described by Fodor et al. from Affymetrix U.S. Pat. No. 5,405,783, a photo-

deprotection step is used where the protecting group on the phosphoramidite is removed by exposing a photosensitive protecting group to light. Four photo masks are used to create patterns to de-protect areas of the substrate and then a nucleotide is added to these regions. This technique requires four masks for each layer of nucleotides. While this technique allows for the production of high-density oligonucleotide arrays, it is less efficient than traditional phosphoramidite synthesis chemistry. With efficiencies of about 90 to 95 percent, the percentage of full-length oligonucleotides within a feature is further reduced to about 9 to 27 percent for oligonucleotides that are 25 nucleotides long (0.90^{25} to 0.95^{25}).

Carrico, (US Patent 5,200,313) similarly identifies problematic aspects of hybridization reactions:

1. The purity of the nucleic acid preparation.
2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.
5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

Art Unit: 1634

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

While applicant has asserted that the claimed device could be used in conjunction with an Arrayed Primer Extension (APEX) assay, the specification does not teach how such technology is to be adapted such that it would be useable in this arguably non-obvious device. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

“‘[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.’ *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) (‘[T]he scope of the claims must bear a reasonable

Art Unit: 1634

correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.'). Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

"It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (emphasis added)

6. Having carefully reviewed the disclosure, finding but limited prophetic teaching of how the device could possibly be used and not finding how art-recognized problems could be overcome and not finding any starting materials or reaction conditions, the specification has not been found to enable the use of the claimed device.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 18-21, 23-27, 30, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, and the charge couple device.

10. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, the charge couple device, and a transparent hexahedron.

11. Claim 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: that which supports and causes the hexahedron to rotate on an axis that is perpendicular to each laser beam. As presently worded, it would appear that the transparent hexahedron is floating in space and is rotating without any input of energy.

12. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural

Art Unit: 1634

cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, the charge couple device and an optical wedge and what means are used to support same and to cause the wedge to revolve around an axis approximating each laser beam.

13. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, the charge couple device, a cylindrical lens and an optical wedge.

14. Claim 21 recites the limitation "said optical wedge" in line 5. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, the charge couple device and the mirror.

16. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, and the diffraction grating.

17. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, and an optical prism.

18. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, and the transparent liquid. It is also unclear as to what contains the liquid.

19. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that which exists between the light source, the waveguide support, the means for directing the lasers, and the bandfilters

20. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the light source, waveguide, the transparent hexahedron, optical wedge, cylindrical lens and mirror.

21. Claim 31 provides for the use of the device, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

22. Claim 31 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless —

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

24. Claims 18, 20, 21 and 26 are rejected under 35 U.S.C. 102(e) as being e by Herron et al. (US Patent 6,316,274 B1).

25. For purposes of examination, the term "cylindrical" (claim 21) has been interpreted as encompassing all forms of a cylindrical lens, including, but not limited to semi-cylindrical lens.

26. Herron et al., column 3, disclose a device comprising a waveguide that has a biological molecule attached to a surface of the waveguide; that the device comprises a semi-. Column 4

discloses the presence of a light source and that it is configured to deliver light into the waveguide. Also disclosed herein is the presence of detection means that allow for fluorescent signals to be collected. Column 5, second paragraph, specifically identifies a CCD. Column 7 discloses the presence of filters such as bandpass. Columns 7 and 8 both teach of the use of a laser.

27. Column 12 discloses the presence and use of a "serrated or toothed shaped" edge. Such is considered to meet a limitation of an optical wedge in that the serrated edge serves to cause the light to enter the waveguide and undergo internal reflection.

28. In view of such teachings in the prior art of record, the invention of claims 18, 20, 21 and 26 are rejected under 35 U.S.C. 102(e).

Conclusion

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

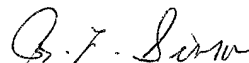
30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Application/Control Number: 09/741,960

Page 13

Art Unit: 1634

31. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS

February 4, 2003